

Diagnosing Colorectal Carcinoma: Clinical and Molecular Approaches

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Introduction

Colorectal carcinoma is the fourth most prevalent carcinoma and second most frequent cause of death from cancer in the United States, with an estimated 131,200 new cases and 54,900 deaths in 1997.¹ Although the death rate from large bowel cancer may be decreasing slightly, it still remains a health risk that consumes national resources and creates considerable personal suffering. Dietary modification may decrease the neoplastic transformation potential of bowel mucosa,² but the widespread adoption of low fat, high fiber diets will not eliminate totally the risk of large bowel cancer. The consumption of aspirin^{3,4} or other nonsteroidal anti-inflammatory drugs⁵ may also reduce the risk of developing the adenomatous polyps that precede large bowel cancers. However, not all patients benefit

from these chemoprevention strategies and some may have deleterious side effects. Recently, fecal occult blood testing (FOBT) and large bowel endoscopy have been found to detect cancers at an earlier stage and decrease the formation of colorectal carcinomas. Also, the recent identification of specific genetic mutations that cause two different types of inherited colorectal carcinoma suggests that in the near future early diagnosis will be possible through blood or stool tests. As a result, considerable enthusiasm now exists that both the rate of earlier diagnosis and the outcome of colorectal carcinoma will be improved.

This review first assesses the common patterns of presentation of colorectal carcinoma, then summarizes the current status of clinical diagnostic methodology, and finally outlines the future potential of molecular diagnostic tests. Critical to the successful application of molecular diagnostic tests is an appropriate understanding of the clinical background within which the tests will be used. Initially, this review focuses on the clinical presentation of colorectal carcinoma, then considers the genetic and biologic causes of colorectal carcinoma. Any molecular approach to diagnosis must explain the range of clinical and pathologic features involved in the manifestations of the disease at presentation. Currently, more patients are diagnosed because they develop signs or symptoms of colorectal cancer than are identified in an asymptomatic state. A major goal is to increase the proportion of patients who are diag-

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Table 1
Conditions Associated with Colorectal Carcinoma

Clinical

Rectal bleeding (occult or clinical)

Abdominal, pelvic, or back pain

Obstruction or perforation

Inflammatory bowel disease

Pelvic radiation

Genetic

History of colorectal carcinoma

History of adenomatous polyps

History of two or more first-degree relatives with bowel cancer

Familial adenomatous polyposis, hereditary nonpolyposis colon cancer,
or variant syndromes

History of breast, ovarian, or endometrial carcinoma

nosed while they are asymptomatic because these patients present at an earlier stage that is more amenable to cure.⁶

Common Patterns of Clinical Diagnosis

The clinical and genetic conditions associated with the development of colorectal carcinoma (Table 1) represent the situations in which the clinician should consider the diagnosis of colorectal carcinoma. Although it is difficult to identify the fraction of patients who are symptomatic at diagnosis, analysis of a large number of patients who are diagnosed in hospitals across the country is informative because it demonstrates the distribution of stage at diagnosis. The National Cancer Data Base (NCDB), a national cancer management and outcomes data base that is a joint effort of the American Cancer Society and the American College of Surgeons,⁷ currently captures more than 50 percent of the estimated new cases of cancer in the United States and is an ex-

cellent starting point for an analysis of the patterns of care and outcome for patients with cancer. Data on the interaction of age, ethnicity, site of primary carcinoma, and stage at presentation are presented in Table 2. As reported earlier in a study of colon cancer,⁸ patients over the age of 70 years are more likely to present with stage I or II disease than are younger patients. This trend is also present in rectal cancer, in which 62 percent of patients over 80 years of age have stage I or II disease compared with 50 percent for those patients who are less than 50 years old and 53 percent for those who are between 50 and 60 years old (Table 2). Ethnicity is another significant factor because African Americans are less likely to present with stage I or II colon or rectal cancer than are non-Hispanic whites (Table 2). Hispanics are also slightly less likely to be diagnosed with stage I or II colorectal carcinoma than are non-Hispanic whites (Table 2). However, Asians have a pattern of stage at diagnosis similar to that of non-Hispanic whites (data not shown),

Table 2
Distribution of Adenocarcinoma of the Colon and Rectum
by AJCC Stage, Age at Diagnosis, and Ethnicity of Patients
Diagnosed in 1993 at Hospitals
Participating in the National Cancer Data Base

Site and Category	% Distribution by Stage			Total %	Number of Cases
	I-II	III	IV		
Age					
Colon					
< 50	44	27	29	100	2,503
50–59	47	27	26	100	4,130
60–69	53	26	21	100	9,112
70–79	57	25	19	100	12,871
≥80	59	25	16	100	8,661
Subtotal					37,277
Rectum					
< 50	50	33	17	100	1,338
50–59	53	30	17	100	2,406
60–69	58	27	15	100	4,273
70–79	59	26	15	100	4,579
≥80	62	22	16	100	2,238
Subtotal					14,834
Ethnicity					
Colon					
Non-Hispanic white	55	25	20	100	32,463
Hispanic	51	29	20	100	680
African American	48	27	25	100	3,087
Subtotal					36,230
Rectum					
Non-Hispanic white	58	27	15	100	11,731
Hispanic	53	27	20	100	372
African American	54	25	21	100	950
Subtotal					13,053

AJCC = American Joint Committee on Cancer.

and the sample of Native Americans is too small to draw any conclusions about their stage at presentation. The data in the NCDB do not reveal any significant effects of median income, region of the country, or type of hospital on the stage of disease at diagnosis (data not shown). As a result, these data from the NCDB suggest that age and ethnicity are important factors to consider in the diagnosis of colorectal carcinoma.

IMPORTANCE OF AGE

Age has two contrasting effects on the diagnosis of colorectal carcinoma. Young (less than 40 years old) patients have a worse outcome than middle-aged patients, whereas older (more than 70 years old) patients present with earlier stage of disease. Bacon⁹ first reported that colorectal carcinoma is diagnosed before age 40 in 2 to 6 percent of all colorectal carcinoma patients. The delay in attributing symptoms to a possible colorectal cancer may contribute to the worse outcome.^{10,11} Although several series indicate that there is a worse outlook for patients who develop colorectal carcinoma before the age of 40,¹²⁻¹⁷ two series^{18,19} suggest that younger patients have the same survival as older patients, possibly because the distribution of patients with stage III and IV disease was similar to that of the older patients in their series.

The outcome of younger patients may be worse because they present with more advanced disease or disease with a poorer histologic grade of differentiation. Several authors^{10,12-16} have found that younger patients present with more nodal or visceral metastases than do older patients, as is the case with the current data from the NCDB (Table 2). However, the data of others^{13,14,17,20} suggest that the outcome of younger patients is worse than that of older patients, even when matched by stage.

The frequency of more advanced disease in younger patients may result

from longer delays in diagnosis compared with older patients; however, the frequency of rectal bleeding or abdominal pain in these young patients is similar to that in older patients. Further, Adkins et al¹⁶ observed that eight of the 45 patients were found incidentally during evaluation for other problems, which suggests that the potential delay in detecting a cancer from the onset of symptoms was less than three months. Similarly, in other studies^{18,20} there was no significant difference in symptom duration between young and old patients. In summary, there is a consensus that the disease presents at a more advanced state in younger patients. Therefore, patients who develop colorectal cancer before age 40 in the absence of a defined genetic syndrome, such as familial adenomatous polyposis or hereditary nonpolyposis colonic cancer, may still have an accelerated rate of mutations that may provide clues to the analysis of the genetic mechanisms that cause sporadic colorectal carcinoma.

Older patients with colorectal cancer are defined as older than 75 or 80 years at the time of diagnosis. Comorbid disease and type of presentation may produce a worse outcome. The series of Payne et al,²¹ Wise et al,²² and Hobler²³ suggest that sepsis and complications of surgery may occur more frequently in the elderly population. However, Arnaud et al²⁴ showed that the postoperative five-year survival rate of older patients was similar to that of younger patients. In addition, the three-year²³ and five-year²¹ cancer-specific survivals of patients over the age of 75 were the same as that of younger patients. Interestingly, several authors suggested that more right-sided cancers arise in the elderly than in the slightly younger population.^{18,21} The elderly seem to have a slightly increased frequency of emergency operations, since 7.4 percent of older patients required emergency surgery, compared with four percent for patients younger than 75 years.²¹ Thus, the biologic behavior of cancers is not likely to be

more aggressive in older patients than in patients between 40 and 70 years old.

ETHNICITY AS A DIAGNOSTIC FACTOR

Ethnicity may be associated with an increased frequency of advanced cancer at diagnosis in African Americans. Thomas et al²⁵ suggest that inner-city blacks are diagnosed with colorectal carcinoma at an earlier age than white patients, and that this trend is significantly greater in black males than in white males. Boring et al²⁶ have reported that there has been a significant increase in cancer-specific death rates in both black men and women for colorectal cancer compared with white men and women over the last 30 years. In fact, the cancer-specific death rate declined in white men and women, whereas it increased in black men and women by 47 and 16 percent, respectively.²⁶ Interestingly, when incidence rates are stratified by educational level and socioeconomic status, the incidence of cancer of the colon and rectum is higher for whites than for blacks for each stratification.²⁶ As in the current NCDB data, Boring et al²⁶ observed a trend in which the frequency of localized cancer at diagnosis is lower in blacks (30 percent) than in whites (36 percent). Thus, the poorer outcome may be attributable to more limited access to care. Weaver et al,²⁷ reporting their experience over a 10-year period at Meharry Medical College, found that their black patients tended to present with more advanced disease than did those observed by Boring et al.²⁶ Their experience may also reflect limited access to health care systems. A major challenge for improving early diagnosis is to increase the proportion of stage I and II colorectal cancers diagnosed in African Americans.

PRESENTING SYMPTOMS AND SIGNS

The symptoms and signs of carcinoma of the colon and rectum are rectal bleeding

(either gross blood in the stool or a guaiac-positive reaction on digital rectal examination), abdominal pain, change in bowel habits, nausea, vomiting, abdominal distention, weight loss, fatigue, and anemia. Rectal bleeding may be associated with an improved outcome, possibly because it prompts earlier diagnosis. Various authors²⁸⁻³¹ have observed that rectal bleeding as a presenting symptom was associated with a better overall survival in univariate analyses, but when rectal bleeding was analyzed in multivariate analysis in which it was corrected for stage and site, it either had no effect^{29,31} or became less important as an independent prognostic variable.²⁸ Similarly, Wiggers et al³² found that only 19 percent of patients who presented with rectal bleeding died of disease compared with 33 percent of patients who did not present with rectal bleeding ($P=0.017$). Cappell and Goldberg³³ observed that rectal bleeding was 2.8 times more prevalent at the time of diagnosis in early stage I lesions than in stage IV cancers. Also, Graffner and Olsson³⁴ reported that rectal bleeding was more frequently associated with rectal (50 percent) than colon (14 percent) cancer. Thus, rectal bleeding may be associated with early stage lesions (perhaps because early lesions are more vascularized than more advanced lesions) and, as a result, may carry a better prognosis. Thus, blood on the stool on digital rectal examination, on guaiac test, or by history must be further evaluated and not dismissed as caused by hemorrhoids.

Abdominal pain is another symptom that may lead to the diagnosis of large bowel cancer. Two types of abdominal pain are caused by cancer of the colon or rectum. The first is cramping or colicky pain associated with complete or partial bowel obstruction. Although uncommon in rectal cancer, it may be a presenting symptom in colonic cancer. This symptom may be best considered as representing the clinical syndromes of obstruction or perfora-

tion that are discussed later. Wiggers et al³² identified abdominal pain and change in bowel habits as significant covariates in their multivariate analysis of patients with colorectal carcinomas.

Either pelvic pain or tenesmus may be a symptom of a locally advanced rectal cancer and may be caused by involvement of peripheral nerves.³⁵ Such a locally advanced rectal cancer may be successfully treated with a multimodality approach. However, pain is more likely to be associated with a stage III than a stage I lesion and, as a result, may have a worse prognosis. Other complaints, such as nausea, vomiting, anorexia, and weight loss of more than 5 kg, are uncommon at presentation but are more likely to be associated with advanced than early stage cancers.³³

Finally, hemorrhoids at presentation may not be associated with survival but may be associated with early stage cancers of the colon.³³ These data reinforce the need to evaluate the entire colon when a patient presents with rectal bleeding and hemorrhoids.

Anemia secondary to microscopic bleeding (e.g., iron deficiency anemia), especially from a right-sided colonic cancer, may be a bad prognostic factor, particularly when it is associated with fatigue and weight loss because it is associated with a fivefold increased risk of metastatic disease.³³

In summary, rectal bleeding may be associated with early stage disease and better survival. Complete or partial bowel obstruction often adversely affects outcome. Constitutional signs and symptoms—such as general malaise, weight loss, and profound anemia—are often associated with advanced disease and reflect the poor outcome of patients who present with visceral metastases.

OBSTRUCTION AND PERFORATION

The definitions of both obstruction and perforation are either imprecise or not

stated. Much of the literature either assumes that the reader knows what an obstruction is or does not indicate whether obstruction is complete (i.e., total absence of flatus or bowel movements for at least a day) or partial. Similarly, the type of perforation (e.g., free into the peritoneal cavity or contained, occurring through the cancer or proximal to a complete obstruction) is often not well described. The incidence of complete obstruction appears to range between two and 16 percent of newly diagnosed cases of colorectal cancer.^{20,26,36} The location of the primary cancer may affect the probability of developing a complete obstruction. Levien et al³⁷ found that carcinomas of the splenic flexure were more likely to obstruct than were carcinomas at other sites. In contrast, obstruction from rectal cancers appears to be uncommon.³⁸ Fielding et al³⁹ suggest that the proportion of patients with obstruction follows the incidence of cancer at each site, whereas other reports suggest that the left colon³⁶ or the ascending colon³⁸ is the most frequent site of obstruction.

The importance of bowel obstruction is supported by its function as an independent covariate in a multivariate analysis of outcome, even with stage included in the analysis. Crucitti et al⁴⁰ studied 361 patients with colonic or rectal cancer and found that the presence of obstruction was a significant predictor of death from cancer even when stage was included in the analysis (obstructed patients had a 31 percent five-year survival compared with a 72 percent survival for patients who were not obstructed). Similar findings have been reported by others.^{29,36,41,42} Wolmark et al⁴² suggested that the development of obstruction added to the poorer prognosis of right-sided colonic cancer, but there was no difference in outcome between right-sided and left-sided colonic cancers in the Gastrointestinal Tumor Study Group colonic adjuvant therapy trials, although in that study the presence of obstruction increased the risk of death from cancer 1.4-fold. Perforation occurs

less commonly. Approximately three-quarters of patients operated upon emergently had obstructions, whereas one-quarter had perforations.⁴³ Among the patients with perforations, only one-quarter of perforations were in the prestenotic bowel or the dilated cecum; most were through the tumor. Of the perforations, half were free perforations into the abdominal cavity, and the remainder were perforations into either an abscess cavity or a phlegmon. Interestingly, five percent of patients had perforations on more than one occasion. Perforation appears to be associated with local recurrence of disease, most likely because malignant cells are dispersed throughout the area of infection.^{28,41} Perforation increases the risk of death from cancer 3.4-fold.²⁸ These different patterns of presentation change the distribution of pain and must be taken into account by the clinician.

ROLE OF INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease is a premalignant lesion that causes a predisposition to colorectal carcinoma when the disease enters a chronic, active phase.⁴⁴ The propensity with which carcinoma develops may be associated with the degree of dysplasia caused by the inflammatory process.⁴⁵⁻⁴⁷ Although chronic ulcerative colitis has long been associated with an increased risk for the development of invasive carcinoma, recent studies have shown that chronic Crohn's disease is also associated with the subsequent development of cancer.⁴⁸ As a result, among the symptomatic patients it is important to remember that inflammatory bowel disease may lead to bowel cancer. The cumulative incidence of colorectal cancer in inflammatory bowel disease is estimated to be five to 10 percent at 20 years and 12 to 20 percent at 30 years.⁴⁸ This reinforces the need for surveillance in patients with inflammatory bowel disease to ensure early diagnosis.

Current Status of Diagnosis in the Asymptomatic Patient

BIOLOGY OF FAMILIAL AND SPORADIC COLORECTAL CARCINOMA

The pioneering work of Muto, Bussey, and Morson⁴⁹ revealed that the majority of colorectal carcinomas develop from an adenomatous polyp. This polyp-to-carcinoma sequence is based on several descriptive but supportive findings: adenomatous polyps have a distribution of location similar to that of cancers that arise in the large bowel^{49,50} but appear an average of five years earlier than does large bowel cancer,^{49,51} many large bowel cancers display remnants of the polyp adjacent to the primary cancer, serial biopsy of polyps that have not been resected reveals a slow process of transformation to an invasive cancer,^{49,52} endoscopic removal of adenomatous polyps decreases the risk of developing bowel cancer by 76 to 90 percent,⁶ and natural history studies of small polyps left in the colon reveal that some polyps less than 0.5 cm in diameter may regress whereas others either remain unchanged or slowly progress to a larger more dysplastic phenotype.⁵³ Cannon-Albright et al⁵⁴ have estimated that 19 percent of the general population forms adenomatous polyps and, therefore, is at risk to develop colorectal carcinoma.

Three recent findings have markedly advanced our understanding of the relationship between the formation of adenomatous polyps and invasive carcinomas. First, the lesion that precedes the development of a polyp is an aberrant crypt focus (ACF) that becomes a microadenoma. The ACF begins as an outpouching of an epithelium-lined sac from the side of the crypt of Lieberkuhn that expands and eventually develops into a separate broad-mouthed crypt.⁵⁵ Microadenomas are identified by methylene blue dye staining at colonoscopy or in the pathology specimen because their crypt openings to the lumen of the bowel are several

times larger than the normal crypt opening.⁵⁶ Roncucci⁵⁶ has reported that microadenomas may be dysplastic, whereas others^{57,58} have shown that loss of tumor suppressor genes and activation of proto-oncogenes may occur with frequencies similar to these events in polypoid adenomas. ACF and microadenomas are important because these lesions develop into adenomas and carcinomas in animal models of carcinogenesis.⁵⁹ However, the evidence that ACFs develop into adenomatous polyps is circumstantial: patients with familial adenomatous polyposis (FAP) have more ACFs than do patients with sporadic colorectal carcinomas, who have more ACFs than do controls without cancer.⁶⁰ Thus, ACF may be an important intermediate marker to aid in the diagnosis of patients with colorectal cancer.

The second finding is that not all adenomas are exophytic; they may be flat and difficult to detect on colonoscopy. The Japanese have focused on the flat adenoma⁶¹⁻⁶⁴ as a precursor lesion to carcinoma; many flat adenomas are ulcerated lesions that may be more aggressive than exophytic cancers.⁶⁵ These lesions have also been appreciated in European patients.⁶⁶ Further, flat adenomas may be precursors to the cancers that develop in hereditary nonpolyposis colorectal cancer (HNPCC) because they display the microsatellite instability that is observed in HNPCC and have a proximal large bowel distribution.⁶⁴ Lynch and his associates have identified several kindreds of patients who display the hereditary flat adenoma syndrome (HFAS) in which colon cancers develop at a later age than in FAP patients, have a proximal colon distribution, and arise in association with flat adenomas.⁶⁷ However, genetic linkage studies suggest that these kindreds are linked to deletions on chromosome 5q and may be variants of FAP rather than altered presentations of HNPCC, which has prompted the use of the term *attenuated familial adenomatous polyposis* (AFAP) for this syndrome.⁶⁸

The third observation is that a fraction of bowel cancers appear to arise without an antecedent polyp. Several reports have suggested that adenocarcinomas of the bowel may arise without polypoid remnants or altered adjacent mucosa.^{69,70} Bedenne et al⁷¹ demonstrated that ulcerated, infiltrating cancers in the right colon were least likely to be associated with an adenomatous polyp. These and other results suggested to Jass⁷² that 10 to 30 percent of colorectal cancers may not develop from an antecedent adenomatous polyp but arise *de novo* from mucosa that appears otherwise normal or has microadenomas. This is important because the current technology for diagnosis in asymptomatic individuals requires that a polyp be removed in order to prevent bowel cancer. As a result, under the present screening guidelines somewhere between 70 and 90 percent of large bowel cancers may be identified and removed before they become frankly invasive. However, under the best of circumstances 10 to 30 percent of large bowel cancers may not develop from a benign polyp and, as a result, may not be detectable or treatable until the lesion is frankly invasive.

MOLECULAR PATHWAYS FOR SPORADIC AND INHERITED COLORECTAL CARCINOMAS: IMPORTANCE FOR DIAGNOSIS

Current evidence indicates that colorectal carcinoma develops through as many as three related but slightly different molecular pathways. The first and best described molecular pathway involves mutation in a gene called the *adenomatous polyposis coli* (APC) gene. This mutation causes the appearance of hundreds to thousands of adenomatous polyps in the large bowel and is the cause of the autosomally dominantly inherited FAP and related syndromes.⁷³ The molecular alterations that occur in this pathway largely involve deletions of alleles of tumor sup-

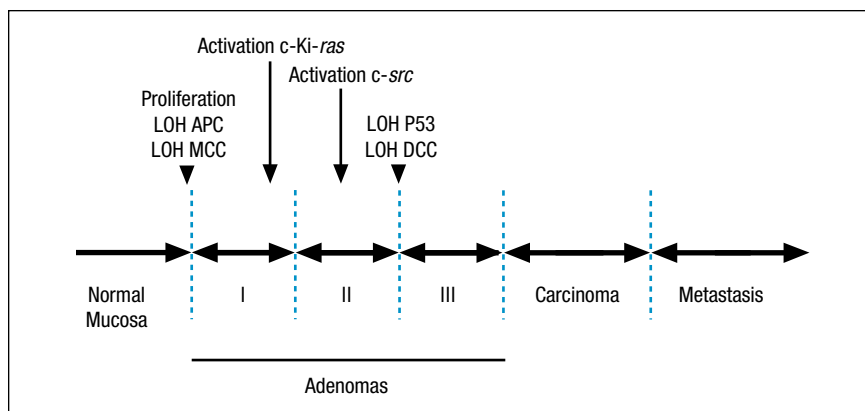


Fig. 1. Genetic alterations in the familial adenomatous polyposis (FAP) type of neoplastic transformation of bowel epithelium. Activation generally implies a mutational event, although it may merely be an increase in the expression of a normal gene product or the dephosphorylation of a peptide such as c-src. APC = adenomatous polyposis coli gene; DCC = deleted in colorectal cancer gene; LOH = loss of heterozygosity. (Reproduced with permission from Jessup et al.⁷⁶)

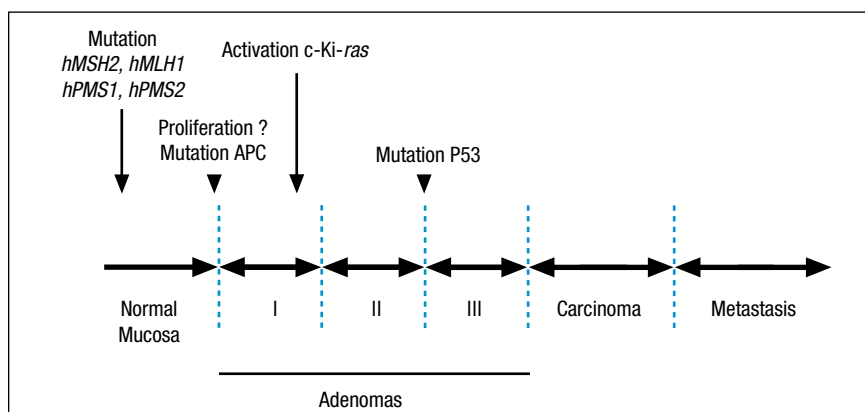


Fig. 2. Genetic alterations in the hereditary nonpolyposis colorectal carcinoma (HNPCC) type of neoplastic transformation of bowel epithelium. Unlike the events in Fig. 1, mutation without loss of heterozygosity occurs in the adenomatous polyposis coli (APC) gene, p53, and c-Ki-ras in this pathway. The passage through the various classes of adenomas may be shortened. (Reproduced with permission from Jessup et al.⁷⁶)

pressor genes, that is, loss of heterozygosity (LOH) in APC, p53, and the deleted in colorectal cancer (DCC) gene⁷⁴ combined with mutational activation of proto-oncogenes, especially c-Ki-ras (Fig. 1; see also reviews in the literature^{75,76}). In

contrast, mutation of the human homologues of the bacterial *mutHLS* complex (*hMSH2*, *hMLH1*, *hPMS1*, and *hPMS2*) produces the DNA mismatch repair defects that appear to be the cause of HNPCC.⁷⁷⁻⁸² The mutations in DNA mis-

match repair enzymes lead to genetic instability that is reflected in errors in accurate replication of the repetitive di-, tri-, and tetranucleotide repeats that are scattered throughout the genome.⁸³⁻⁸⁶ As a result, the genomic instability identified in HNPCC is commonly referred to as either *replication error positive* (RER+) or, because microsatellite regions in the genome contain the nucleotide repeats, as *microsatellite instability* (MIN). Although these replication errors produce mutations in many of the same tumor suppressor genes and proto-oncogenes that are affected in the FAP pathway, there is a significantly lower frequency of LOH in the HNPCC pathway⁸⁵ (Fig. 2).

Finally, although many sporadic carcinomas appear to follow either the FAP (with mutation and LOH of APC, p53, and DCC) or the HNPCC (with RER+ phenotype and mutation of APC, p53, and DCC without LOH) pathway, colorectal carcinomas that arise de novo seem to have a slightly different pattern of molecular alterations that may suggest a third, yet to be defined molecular pathway. De novo carcinomas may have rates of mutation in the p53 gene⁸⁷ similar to those of carcinomas that arise in association with adenomatous polyps but do not appear to contain c-Ki-ras mutations.⁸⁸ Interestingly, the expression of the intestinal mucin gene product MUC2 seems to be lost in de novo carcinomas but is retained in both mucinous cancers and carcinomas arising from polyps.⁸⁹ These studies with de novo colorectal carcinomas need to be better developed before the de novo carcinoma is accepted as another molecular pathway for neoplastic transformation (Table 3).

FAMILIAL ADENOMATOUS POLYPOSIS SYNDROMES AND THE APC GENE

Familial adenomatous polyposis syndrome is associated with loss of APC, a tumor suppressor gene on chromosome 5q21.⁷³ Cytogenetic analyses implicated loss of

material on the short arm of chromosome 5 (5q) as occurring frequently in patients with familial adenomatous polyposis⁹⁰ and the APC gene has been unambiguously identified.⁹¹⁻⁹³ The affected gene is the earliest identified primary genetic change in development of adenomas and is present in adenomatous polyps with a diameter of 5 mm.⁹⁴ The gene is also mutated in sporadic tumors and in other familial syndromes such as Gardner's syndrome.⁹¹ The function of APC is not completely understood, but parts of the sequence are homologous with such structural proteins as myosin and keratin.⁹³ Some similarities have been noted between APC and the GTPase activating protein (GAP), which regulates the *c-ras* gene products, suggesting a potential role for this gene in signal transduction processes.⁹⁴ APC also binds β -catenin, which implicates it in cell adhesion events because the catenins are essential for the function of the intercellular adhesion molecule cadherin.^{95,96} In addition, APC binds to microtubules.⁹⁷ Mutations of APC are generally either point mutations or insertions of mobile genetic elements that lead to chain termination and production of truncated proteins.^{98,99}

Further studies are required to understand the function of the protein and the significance of the different locations of mutations. For example, Gardner's syndrome is thought to be a variant of the familial adenomatous polyposis syndromes, with distinct pathologic manifestations in which extracolonic tumors develop in addition to adenomatous polyps. Yet identical mutations are found in the classic familial adenomatous polyposis syndromes and Gardner's syndrome, suggesting that the different phenotypes are the result of other genetic alterations. Nevertheless, the location of the mutation may influence the number of adenomatous polyps produced.^{68,100-105} The cloning of the APC gene presents powerful diagnostic opportunities, particularly for individuals with a family history of

Table 3
Molecular Alterations in the Three Pathways
for the Development of Colorectal Adenocarcinomas

Pathway	Genetic Type	Adenoma (Number)	Conversion to Cancer (%)	Mutation Type	% Mutation			MUC2 Expression
					APC	c-Ki-ras	p53	
FAP ¹	Inherited	Polypoid (10 ² –10 ³)	1–5	LOH	~100	90	70	ND
HNPCC ²	Inherited	Flat (1–5)	50	RER+	70	70	70	ND
Sporadic-FAP ³	Somatic	Polypoid (1–10)	1–5	LOH	~70	70	70	50%
Sporadic-HNPCC ⁴	Somatic	Flat (1–3)	50	RER+	~70	70	70	ND
Sporadic-de novo ⁵	Somatic	None	100	ND	~70	0	70	0%

¹Autosomally dominant disorder that produces hundreds to thousands of adenomatous polyps, only 1 to 3 of which may become malignant during the course of an individual's lifetime.
²Autosomally dominant inherited disorder that causes cancer in patients with only a few flat adenomas.
³Cancer that arises often in association with an adenomatous polyp; not caused by an inherited mutation in the APC gene but has a high incidence of mutation in APC through somatic mutation.
⁴Cancers that arise in the colon proximal to the splenic flexure and are often RER+, contain somatic mutations in a DNA mismatch repair gene, and arise with only a few flat adenomas.
⁵Cancers that arise without an adjacent adenoma and that may contain somatic mutations in the APC gene but that are RER-.

APC = adenomatous polyposis coli
HNPCC = hereditary nonpolyposis colorectal carcinoma

FAP = familial adenomatous polyposis
ND = not determined.

colon cancer. Because this gene is altered in the germline or in all the cells of the body in patients with FAP, screening in the future will involve simply collecting peripheral blood cells to detect APC mutations. However, this blood test will not identify patients who are at risk for developing sporadic bowel adenomas. The recent description of identifying mutations in *K-ras* by amplifying DNA isolated from stool through the use of the polymerase chain reaction (PCR) technology¹⁰⁶ may allow for similar approaches to the analysis of stool from patients at risk for the development of adenomatous polyps. Because 75 percent of adenomatous polyps have a mutation in APC,⁷⁴ stool may contain sufficient mutant APC

DNA to be isolated and identified. Additionally, as the function of the gene product of APC is better understood, important insights are likely to be gained into the molecular basis for the development of adenomas.

HNPCC: AN ALTERNATIVE PATHWAY

The HNPCC syndrome represents an alternative pathway for the induction of colorectal carcinomas. As described by Lynch and colleagues,^{107,108} this is a syndrome characterized by the development of colon cancer, usually in the proximal colon, in three first-degree relatives in two generations with at least one of the colon cancers occurring in a person

younger than 50 years.¹⁰⁹ Two variants of the syndrome are recognized: Lynch syndrome I, in which carcinomas are limited to the colon, and Lynch syndrome II, which has extracolonic carcinomas in such sites as the endometrium, breast, biliary tract, and pancreas, as well as in the proximal colon. Each syndrome may have a few adenomatous polyps present when the carcinoma is detected, but the number of polyps is usually less than five,¹¹⁰ and the polyps often appear as the cancer is diagnosed.¹⁰⁸ The lack of preneoplastic lesions or associated stigmata (e.g., the osteomas and epidermoid cysts of FAP patients) combined with variable penetrance of this autosomal dominant disease make identification of individuals at risk difficult. This is important because screening family members with colonoscopy and endometrial cytology is time consuming, difficult, and expensive. In addition, the prevalence of this syndrome is estimated to be between three and 8.5 percent of colorectal carcinomas^{107,111} compared with the one percent prevalence of the FAP syndrome.¹¹² These estimates may be high because a recent population-based study from Finland¹¹³ indicates that 2.4 percent of colorectal cancers are HNPCC-related, 1.0 percent are secondary to ulcerative colitis, 0.7 percent are FAP-related, and 3.4 percent arise in patients who had previously had colorectal carcinoma. Thus, HNPCC is a bigger health risk than FAP and identification of the gene responsible for HNPCC may be important for screening individuals at risk more efficiently and cheaply.

A number of studies have been performed to determine whether HNPCC patients display genetic markers in the bowel epithelium or elsewhere that distinguish affected individuals from those who develop sporadic colorectal carcinomas or who have FAP. Patients with FAP have an extension of the DNA synthetic zone into the apical portion of the crypt of Lieberkuhn.^{114,115} Individuals with HNPCC

as a group do not appear to have any changes in either the number of cells proliferating or the size of the proliferating cell compartment in the crypt compared with normal individuals who are not predisposed to develop colorectal carcinoma.¹⁰⁷ Although a subset of HNPCC patients have high mucosal proliferation indices and an expansion of the proliferating cell compartment into the apex of the crypt in random rectal mucosal biopsies, it is unlikely that patients can be identified by rectal mucosal proliferation studies.

Vogelstein, de la Chapelle, and their colleagues attempted to link the standard tumor suppressor genes with affected individuals in several HNPCC kindreds but soon found that APC, p53, and DCC did not undergo LOH and were not associated with HNPCC^{83,84} (Fig. 2). Another type of gene marker, microsatellite DNA, then became available as part of the human genome mapping project. The human genome contains between 50,000 and 100,000 highly repetitive di-, tri-, and tetranucleotide segments of DNA that display length polymorphisms and may be used for gene linkage analysis.¹¹⁶ When Vogelstein, de la Chapelle, and their colleagues surveyed a large number of these microsatellite markers, they found that marker D2S123 on chromosome 2p was linked with HNPCC in two large kindreds.⁸³ This was important because the defective gene did not undergo loss of heterozygosity in the two kindreds in which linkage was established.

These microsatellite DNA markers are not only useful for identifying a possible locus for the HNPCC gene but are themselves modified by the disease process. Simultaneously and independently, Aaltonen et al.⁸⁴ Thibodeau et al.,⁸⁵ and Ionov et al.⁸⁶ found that these short stretches of di- and trinucleotide DNA repeats could undergo amplification or deletion. Aaltonen et al.⁸⁴ found that the microsatellite marker D2S123 was altered in 10 of 13 HNPCC tumors, including one individual whose cancer did

not appear to be linked to the D2S123 marker. Further, the amplification or deletion of nucleotide repeats was not limited to the D2S123 marker but also was present in other microsatellite markers, some of which were located far from the D2S123 marker on other chromosomes. In addition, alteration of microsatellite marker repeats was present in six of 23 sporadic right colon carcinomas but none of 23 sporadic left colon cancers. Thus, some sporadic right-sided colon carcinomas may arise by the same mechanism as the right-sided colon carcinomas observed in HNPCC.⁸⁴ Further, these alterations in the number of microsatellite dinucleotide repeats were associated with an improved survival.⁸⁵ Ionov et al⁸⁶ confirmed that other di- and trinucleotide DNA repeat markers were also present in right colon cancers. Similar alterations in microsatellite DNA have now been identified in endometrial, gastric, and pancreatic carcinomas.¹¹⁷⁻¹²⁰ Taken together, alteration in microsatellite DNA repeats indicates an increase in genetic instability that arises from an impairment in the repair of DNA nucleotide mismatches.

But what about the genes involved? Because the defect noted in HNPCC appeared to be an error in DNA replication, Kolodner and his colleagues at the Dana-Farber Cancer Institute considered that it resembled a defect in yeast and bacteria that occurs when genes that encode proteins that repair dinucleotide mismatches are mutated. In bacteria this repair system requires the cooperation of several proteins in the MuthLS pathway that depends upon the *mutH*, *mutL*, *mutS*, and *mutU* gene products to bind to mispaired nucleotides during replication, excise the nucleotide, then replace it with the correct nucleotide.¹²¹ Kolodner and his colleagues⁷⁷ found a homologue to the *mutS* gene that they termed *hMSH2* on chromosome 2 in the vicinity of the D2S123 marker. They then demonstrated that this gene when mutated caused an increase in the mutation rate of a marker

gene when introduced into *E. coli*. Finally, they showed that seven of 26 sporadic colorectal carcinomas contained the (CA)_n dinucleotide repeat alterations and that two of these seven sporadic tumors had mutations in a conserved portion of the *hMSH2* gene. A survey of small HNPCC kindreds revealed the same heterozygous germline mutation in two of nine kindreds. All five affected individuals surveyed in the two kindreds had the same mutation, whereas two unaffected individuals in one kindred did not have the mutation in *hMSH2*. Although this mutation was not seen in any members surveyed in seven other kindreds, it is possible that other mutations may exist for which these individuals were not screened. Leach et al⁷⁸ have extended these findings to demonstrate that the *mutS* homolog maps to 2p16 and other mutations are found in the gene in several HNPCC kindreds as well as in sporadic proximal colon cancers. Subsequent work has led to the identification of *hMLH1*,^{79,80} *hPMS1* and *hPMS2*,⁸¹ and *GTBP*,⁸² which are all members of the mismatch repair gene family. Although mutations in *hMSH2* and *hMLH1* account for the majority of the mutations identified in kindreds of HNPCC tested so far, all but *GTBP* of the mismatch repair genes are mutated in different HNPCC kindreds identified to date.¹²² Thus, although more homologs of the *mutHLS* complex may exist, 92 percent of the kindreds of HNPCC are RER+ and 70 percent have a mutation in one of the known mismatch repair genes.¹²² This may be used for genetic testing in the future either for inherited defects in the germline, as represented in the cells in the peripheral blood, or in somatic mutations in the DNA released into the stool.

GENETIC ALTERATIONS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE

Analysis of the mutations associated with carcinomas arising in inflammatory bow-

el disease (IBD) suggests that the pattern of genetic mutations and accumulated defects is similar to that of sporadic carcinomas. Mutation and LOH in the p53 gene have been described in both the carcinomas associated with inflammatory bowel disease and the dysplastic mucosa that appears to be the premalignant lesion.¹²³⁻¹²⁵ The question of mutation without LOH, which might be a hallmark of the HNPCC pathway, was raised by Brentnall et al¹²⁶ who demonstrated that LOH for p53 was a late event occurring in 83 percent of cancers arising in colitis compared with dysplasia, in which only 44 percent of lesions had LOH for p53. However, Meltzer and colleagues¹²⁷ found that LOH was a common event in lesions arising in IBD that contained a mutation in one allele of p53. APC mutations have been identified in 50 percent of the cancers arising in IBD patients.¹²³ MIN also occurs in 15 to 20 percent of carcinomas associated with IBD.^{128,129} Thus, both the FAP and the HNPCC pathways may be activated in subsets of these cancers that arise in association with chronic active IBD. The difficulty in determining whether the mutational activity of the HNPCC pathway or the deletional function that generates LOH in the FAP pathway is the predominant mechanism is likely to continue because the number of specimens available for study is limited. Nonetheless, the dysplasia-to-carcinoma sequence that has been considered the pathway for the development of carcinoma in IBD¹³⁰ appears to involve the same tumor suppressor genes and proto-oncogenes present in the sporadic and familial carcinomas.

Classic Approach to Bowel Cancer Screening

Epidemiologic studies have suggested that as many as 19 percent of the general population are at risk to develop adenomatous polyps.⁵⁴ Five percent of sporadic polyps may progress to form colorectal

carcinoma. As a result, screening patients for polyps or early minimally invasive cancers when they can be removed endoscopically or treated easily is likely to decrease the overall mortality from colorectal carcinoma. To date the classic approach to such screening (i.e., the identification of cancers before they become symptomatic) has involved testing for blood in the stool or direct imaging of the bowel either by diagnostic radiologic techniques or by endoscopy. However, it was not until recently that screening was shown to reduce mortality from bowel cancer. The strategies used for screening have been based primarily on FOBT and colonoscopy.

RESULTS OF SCREENING BASED ON FECAL OCCULT BLOOD TEST

As outlined earlier, the presence of blood in the stool may indicate that a polyp or invasive carcinoma is present in the large bowel. Guaiac-based tests to assess the presence of blood in the feces depend on fecal heme to catalyze the phenolic oxidation of guaiac in the presence of hydrogen peroxide to produce a blue chromogen. As reviewed by Ferrante,¹³¹ there are many reasons why guaiac-based tests may give false-positive reactions for blood. Vitamin C ingestion, aspirin and non-steroidal drugs that cause microscopic bleeding from mucosal irritation, peroxidase present in many fresh fruits and vegetables as well as animal hemoglobin and myoglobin may also catalyze the oxidation of guaiac. As a result, FOBT is often performed with subjects on strict diets to minimize false positives. However, this also reduces the compliance of people taking the test. Thus, in most trials that are based on FOBT, there is a trade-off between the false-positive rate and compliance. This has led at least one group¹³² to conclude that FOBT-based screening is not useful. Furthermore, it is clear that the sensitivity and specificity of guaiac-based tests involves whether the test card impregnated with guaiac is rehydrated

before the hydrogen peroxide is added. In most of the older studies¹³³⁻¹³⁶ the Hemoccult card (SmithKline Diagnostics, San Jose, CA) is not rehydrated and the percentage of positive tests varies between 1.1 and 2.3 percent. Rehydration of the Hemoccult card increases the positivity rate to 5.8 to 9.8 percent.¹³⁷ However, rehydration is associated with a decrease in the specificity of the Hemoccult test from 96 to 99 percent¹³³⁻¹³⁵ to 90 percent.¹³⁷ In large trials that involve tens of thousands of subjects this decrease in specificity substantially increases the number of colonoscopies that must be performed and increases the cost of a screening trial.

Nonetheless, screening for large bowel cancer is beginning to demonstrate its utility in reducing mortality from colorectal carcinoma. Screening for blood in the stool does not affect the underlying process of neoplastic transformation in the large bowel. The number of cancers found in the bowel is the same in the screened group as it is in the control group. However, the screened subjects should have less advanced cancer at diagnosis than the control group and, as a result, should have less mortality from colorectal cancer. An increase in the proportion of earlier stage cancers has been observed in several FOBT trials, but it is associated with a significant reduction in cancer-specific mortality in only one prospective, randomized trial, the Minnesota Colon Cancer Control Study,¹³⁷ because the other trials are not yet mature. In the Minnesota study, subjects were randomized to annual or biennial FOBT tests or to a control group. The underlying incidence of colorectal cancer was not affected because the cumulative incidence of bowel cancer was 23, 23, and 26 per 1,000 subjects in the three groups, respectively. However, after 13 years of follow-up, the annually screened group had a cumulative mortality from colorectal cancer that was 5.88 per 1,000 compared with 8.33 and 8.83 per 1,000 for the

biennially screened and control groups, respectively. The reduction in mortality was associated with a significantly lower stage at diagnosis in the annually screened group, with only 33 stage IV cancers in the annually screened group compared with 41 and 65 for the other two groups. This trial introduced rehydration of the Hemoccult II slides part way through the study, which increased the FOBT positivity rate from 2.4 percent to 9.8 percent. This significantly increased the number of colonoscopies that were performed. In addition, nearly half of the cancers that were found in each group were found between screening visits. Those cancers that were found because of symptoms in either the annually or the biennially screened group had a worse survival that was similar to that of the control group. These data suggest that cancers found through screening may be slower growing, less likely to be aggressive, or at an earlier stage. In contrast, the cancers found between screenings may be more invasive and are likely to have advanced to a higher stage. Another unexplained aspect of this study is that polypectomy in the screened groups has not yet had an impact on cancer-specific mortality.

Other randomized trials of FOBT-based screening have shown similar trends in identifying earlier stage disease and better cancer-specific survival. The Memorial Sloan-Kettering Cancer Center-Strang Clinic trial¹³³ showed a trend for earlier stage of lesions at diagnosis; 65 percent of cancers were in stage I or II in patients who had FOBT and sigmoidoscopy versus 33 percent of cancers in the control group that had sigmoidoscopy alone. At 10 years, cancer-specific mortality in the FOBT and sigmoidoscopy group was decreased 43 percent compared with the control group, but this was only a trend ($P=0.053$). In all three European randomized trials, the fraction of colorectal cancers diagnosed as stages I and II increased 6 percent,¹³⁴ 33 percent,¹³⁵ or 9 percent¹³⁶ compared with the

Table 4
Screening Guidelines for Colorectal Carcinoma

Symptoms	Family History	Age to Begin Tests	Evaluation
None	None	50	DRE; stool guaiac; colonoscopy: if negative repeat in 3-5 years, otherwise repeat in 1 year to ensure no new lesions
None	1 or more FDR	40	As above
None	FAP	10	DRE; colonoscopy: repeat annually if polyps found or at 3 years if no polyps
None	HNPCC	Late teens	As for FAP
Present	None	25	DRE; stool guaiac; colonoscopy: if negative repeat in 3-5 years, otherwise repeat in 1 year to ensure no new lesions

Note: Role of genetic testing is not clear at the present time; members of families that have FAP or HNPCC probably should be referred to a clinical center that does genetic counseling.

DRE = digital rectal examination FAP = familial adenomatous polyposis
FDR = first-degree relative HNPCC = hereditary nonpolyposis colorectal carcinoma

control groups. This result supports the possibility that with longer follow-up this earlier stage at diagnosis will translate into a reduction in cancer-specific mortality.

Rehydration increases the cost of screening but increases the sensitivity of the test,^{138,139} which raises the question of whether there are other tests for fecal blood that may enhance the specificity of the methodology and contain the cost of screening. Several recent studies suggest that immunologically based tests for human hemoglobin may enhance the sensitivity of FOBT. Kempainen et al¹⁴⁰ found that an immunologic test for fecal blood when combined with a guaiac-based test increased the sensitivity for detection of cancer in symptomatic patients. Similarly, Robinson et al¹⁴¹ found that the addition of HemeSelect (SmithKline Diagnostics, San Jose, CA), another immune-based fecal blood test, to a mass screening program improved the detec-

tion of cancers, although by itself the test was less specific. Allison et al¹⁴² studied the combination of HemeSelect with the guaiac-based Hemoccult II Sensa test in 8,104 asymptomatic subjects in the Kaiser Permanente Medical Center in Oakland, California, and found that the combination of HemeSelect and Hemoccult had a specificity for detecting carcinoma of 97.7 percent and a sensitivity of 65.6 percent. The combination was significantly better than either test alone. The major difficulty with the immune-based test is that it is more labor intensive and, as a result, somewhat more expensive. Furthermore, the immune-based test by itself appears to be less specific than the guaiac-based tests.

Thus, FOBT-based screening is beginning to have an impact on survival and appears to identify the majority of bowel cancers at a locoregional stage that is amenable to cure by current surgery and adjuvant therapy. A recent meta-analysis

by Towler et al¹⁴³ of the randomized trials indicates that the use of Hemoccult testing is associated with a 19 percent reduction in the mortality rate from colorectal carcinoma. With the introduction of immune-based tests that may enhance the sensitivity and specificity of guaiac-based tests, the costs of screening may also be improved.¹⁴⁴

ENDOSCOPIC SCREENING

Although FOBT-based screening is associated with a reduction in mortality from colorectal cancer, it does not directly alter the biology of neoplastic transformation of the mucosa of the large bowel. The only way to do that is to surgically extirpate the colon and rectum, provide effective chemoprevention with aspirin^{3,4} or other nonsteroidal drugs,⁵ or remove colonic polyps that are the precursor lesions for the majority of colorectal carcinomas. The latter is the easier of the two mechanical approaches to decreasing the incidence of colorectal carcinoma but is relatively expensive. Nonetheless, a recent randomized trial⁶ from the National Polyp Study demonstrates that colonoscopy decreases the incidence of colorectal carcinoma between 76 and 90 percent. This study also showed that two or more adenomas detected at the first evaluation, adenomas that were more than 0.5 cm in diameter, or dysplastic adenomas were factors associated with the subsequent development of both adenomas and carcinomas.¹⁴⁵ Interestingly, only two or more adenomas at first evaluation were associated significantly with the development of carcinoma of the large bowel. Age younger or older than 60 years was not a significant factor.¹⁴⁵ Interestingly, three-year intervals between colonoscopies were as effective as a one-year interval in reducing colorectal cancer development.¹⁴⁵

The role of flexible sigmoidoscopy is not as well established. Removal of adenomatous polyps by a flexible sigmoidoscope to 60 cm from anal verge clearly

controls neoplastic disease within the reach of the sigmoidoscope.¹⁴⁶⁻¹⁴⁹ As pointed out by Selby et al,¹⁵⁰ flexible sigmoidoscopy is less costly than colonoscopy, is safer, and may have a higher degree of compliance. Future studies need to determine whether the identification of isolated adenomatous polyps at flexible sigmoidoscopy should be followed by a full colonoscopy to rule out synchronous polyps elsewhere in the bowel that suggest a higher risk for neoplasia.¹⁴⁵ However, in those patients who have more than one polyp, polyps that are dysplastic or larger than 0.5 cm, or first-degree relatives with colorectal carcinomas, flexible sigmoidoscopy is insufficient. Such patients should have colonoscopy or chemoprevention, or both.

COST-BENEFIT ANALYSES

As in many other prevention and epidemiologic studies, it is difficult to analyze the cost-benefit ratio for screening asymptomatic colorectal carcinoma. The assumptions for any mathematical model are usually uncertain because the true cost of a technology is often hidden and may not be as great as the estimate provided or may be far larger. In the 1980s analyses suggested that screening based on FOBT would not be cost-effective.¹⁵¹ More recent analyses suggest that the costs have been sufficiently reduced so that screening based on FOBT and colonoscopy may be cost-effective.¹⁵² One recent analysis predicted that the average cost of FOBT-based screening was \$834 per person.¹⁵² The average cost of treating advanced bowel cancer that was missed without a screening program was estimated to be \$300 more per person. Johnson and Jolly¹⁵³ found that the actual cost per bowel cancer detected in a sample of 29,786 people was \$9,670. These projections and data suggest that it will be less expensive ultimately to diagnose bowel cancers before they cause symptoms rather than let them develop

into advanced cancers that cause symptoms when large populations of individuals are combined into full-risk capitated contracts.

A recent report from the Health Care Finance Administration¹⁵⁴ suggests that the managed care organizations already are beginning to implement screening programs. Participants in Medicare Health Maintenance Organizations (HMOs) in several cities around the United States who were diagnosed with breast, colon, cervix uteri, rectum, melanoma, prostate, buccal cavity and pharynx, bladder, corpus uteri, kidney, stomach, and ovarian cancers were selected from tumor registry data in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and compared with case controls diagnosed within fee-for-service arrangements. The data indicate that elderly patients in HMOs were diagnosed at earlier stages of disease for breast and colon cancer but not for any of the other cancers. Interestingly, the stage at diagnosis for rectal cancer was not significantly earlier for the HMO participants, although there was a trend in that direction. Although this study is subject to the limitations that it was not a direct assessment of screening techniques or resource utilization and the pitfalls associated with selecting case controls, nonetheless it indicates that patients in HMOs may be diagnosed at an earlier stage for carcinomas in which there are data to support the use of screening.

Current Guidelines for Colorectal Screening

Guidelines for screening asymptomatic patients (Table 4) are based on current practice.¹⁵⁵ Patients who are symptomatic (e.g., rectal bleeding, pain, obstipation, anemia, etc.) should have an appropriate evaluation. Certainly, we see patients without a family history who are in their late twenties but present with locally advanced colorectal cancer after months of

symptoms that were disregarded because of their young age. It is extremely important that symptoms be evaluated aggressively, if only to provide the best opportunity for local control.

Future Potential for Molecular Diagnostic Tests

As FOBT and the invasive, costly colonoscopy begin to decrease the mortality of colorectal carcinoma, are there other alternatives that may be easier to implement for screening? Clearly, familial cancers may be diagnosed by blood tests because the mutation in APC or the DNA mismatch repair genes are present in all the cells of the body (i.e., germline mutations). However, genetic tests are still not ready for accepted clinical practice.¹⁵⁶ The difficulties inherent in genetic testing for inherited cancers have been well described by Li¹⁵⁷ and Petersen and Boyd¹⁵⁸ and will not be reviewed here. As described earlier, this means that approximately 10 percent or less of large bowel carcinomas are amenable to detection by blood tests. Because the rest of the large bowel cancers appear to arise sporadically, it is not clear that any of them are associated with germline mutations; rather, they are caused by somatic mutations that can be found only in the epithelial cells lining the colon and rectum. Thus, fecal studies are still necessary to detect somatic mutations that are associated with an increased risk of invasive cancer. Sidransky et al¹⁰⁶ showed that DNA isolated from stool may be analyzed for the mutations in c-K-ras that are present in approximately 70 percent of colorectal carcinomas.⁷⁴ Technically, it should be feasible to analyze DNA from stool for mutations in APC and possibly DNA mismatch repair genes. Since mutations in these genes occur during neoplastic transformation of the bowel mucosa, cells containing the mutated genes should be shed into the feces and should be able to be amplified and examined. Analysis of

the APC gene may be most appropriate because this gene is mutated in the majority of adenomatous polyps, and a fecal DNA test might theoretically identify adenomatous polyps.

If genetic tests are to be effective screens for colorectal or other cancers, they must be applied to subjects who are at greatest risk for the development of cancer. Probably the best and cheapest method of identifying this cohort is through a detailed family history. Clearly, first-degree relatives are at increased risk for developing bowel cancer, even if they do not appear to be in a FAP or HNPCC family.¹⁵⁹⁻¹⁶² As a result, these high-risk individuals should be candidates for regular screening and, perhaps, should be considered for genetic testing. Accurate family histories of patients with large bowel and other malignancies are probably the most important tools for identifying patients who should be screened by either the classic FOBT and colonoscopy or genetic tests when they become widely available.

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Summary

In summary, the ability to decrease the mortality of colorectal carcinoma is increasingly within the grasp of clinicians. With accurate family and personal history, it is possible to estimate the risk of colorectal cancer and initiate FOBT and colonoscopy where appropriate. In the future, germline and even somatic genetic testing will further increase our ability to diagnose cancers before they become widely invasive. As molecular biology unravels the cause of what currently appears to be the majority of sporadic cancers, it may be possible to characterize more colorectal cancers that are caused by novel, as yet not recognized mutator genes. Unfortunately, a set of patients is likely to exist who remain to be diagnosed by symptoms caused by advanced cancer. The goal for the clinician is to decrease this subset to as small a group as possible. **CA**

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